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TRANSMISSION OF NERVOUS EFFECTS BY ACETYLCHOLINE

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Just four years ago Otto Loewi lectured here on "the humoral transmission of nervous impulse." It was most fitting that he should be the first to lecture to this Society on that subject, since it was through the experiments which he made with his pupils and co-workers, and described in a series of papers published between 1921 and 1926, that such transmission became an experimental reality. Professor Loewi referred in his lecture to some of the speculations and experimental hints concerning such a process, which had anticipated his own now classical demonstration of its occurrence. In that connection he referred to the well-known and fundamentally important observations of Howell (1906, 1908), on the mobilization of potassium ions as a concomitant of vagus inhibition of the heart. I find no evidence, however, that Professor Howell thought of a liberation of potassium ions as occurring at the vagus nerve endings, and transmitting the inhibitory stimulus from them to the heart fibres. I think that it would have been more natural, from his description, to form a conception of the mobilization of potassium in the heart muscle cells, as part of the essential change in those cells, evoked by the vagus impulses and resulting in inhibition of their rhythm. This seems, in any case, to be the proper interpretation of the meaning of Howell's facts, in the light of the now accepted identification of acetyl-

choline, as the transmitter of the effects of vagus impulses from the nerve endings to heart cells. Professor Lehnartz (1936), of Göttingen, working last year as a guest in my laboratory, confirmed Howell's observation of the increase of potassium ions in the Ringer solution filling a tortoise auricle, when the vagus nerves were effectively stimulated. He found, however, that the addition of acetylcholine to the Ringer solution, in a concentration producing a comparable inhibition of the heart rhythm, caused an entirely similar mobilization of potassium ions. He further observed that, when the inhibitor effect of vagus impulses, or of adding acetylcholine to the solution, was prevented by atropine, no potassium ions were released. Clearly the observed mobilization of potassium is part of the inhibitory process in the heart cells, and not of the transmission to them of the vagus effect. The real anticipation, I think, of what Loewi so simply and convincingly demonstrated, is to be found in the speculation current among younger workers in the Cambridge (Eng.) school about the years 1904 to 1906. It started with Elliott's (1904) penetrating suggestion, that sympathetic nerve impulses act on the effector cells by liberation of epinephrine (adrenalin) at the nerve endings. By an obvious analogy the late W. E. Dixon (1906, 1907) extended the suggestion to parasympathetic nerves and muscarine, and even put forward experiments on the heart and the vagus, which purported to demonstrate such a mechanism, but failed to carry conviction. What is remarkable, I think, in retrospect, is the fact that Dixon first described these rather unconvincing experiments at a meeting in Toronto in 1906, at which Reid Hunt also gave the first account of his discovery of the remarkable depressor activity of acetylcholine. Neither, apparently, saw any connection between the two sets of observations. When, however, in 1914, I came across acetylcholine in another connection, and studied its action in greater detail, the obvious relation of that action to parasympathetic nerves, so suggestively similar to the relation between the action of epinephrine and the true sympathetic system, could not but revive interest in ideas

which had, by then, been almost forgotten. We advanced no further, however, than the reflection that, *if* there were direct evidence in favour of Elliott's conception concerning epinephrine and sympathetic action, we should have to think of something like acetylcholine in relation to parasympathetic effects; and there the matter remained till 1921.

Then came Loewi's experiments, and, after the few years necessary for accommodation to a new set of ideas, the transmission of the excitatory, or inhibitory, stimulus from the peripheral endings of autonomic nerve fibres to effector cells, by the liberation of specific chemical stimulators, became a part of the accepted teaching of physiology. Loewi described two different chemical substances, one responsible for the transmission of inhibitor effects from the vagus, the other for that of accelerator effects from the sympathetic nerve endings to the muscle fibres of the frog's heart; and it was impossible not to think of acetylcholine and epinephrine, though there was, at that time, no evidence that acetylcholine even occurred in the body. Cannon and his co-workers (1921, 1931) by a line of investigation having a different object, were beginning to get evidence, about the same time, of something passing into the circulation when certain sympathetic nerves were stimulated, and reproducing sympathetic effects on distant organs. In the intervening years they have published a large volume of observations on these phenomena, full of suggestion and interest, and leading them to the conclusion that the sympathetic transmitter, which they refer to as "sympathin," is not epinephrine itself. On the other hand, there are experiments by Bacq (1933), who took part in Cannon's investigations at an important stage, and most recently by Loewi (1936) himself, which suggest that "sympathin" corresponds with epinephrine, in every character for which it can be tested *in vitro*, and strongly suggest that the two are identical.

When Loewi lectured here in 1933, he had just reached the point of accepting the identity of his *Vagusstoff* with acetylcholine, after some twelve years of doubt and hesitation.

It was not until 1929, indeed, that my late colleague, H. W. Dudley, had first succeeded in isolating acetylcholine as a natural constituent of an animal organ. Loewi's chief obstacle to the identification, however, had been the resistance of certain parasympathetic effects to atropine; though, as I had pointed out, his own brilliant experiments had shown that the *Vagusstoff* was, in any case, an unstable ester of choline, and the atropine difficulty would stand equally in the way of any of these, and even of choline itself. The demonstrated liberation of a substance indistinguishable from acetylcholine, even in connexion with parasympathetic nerve actions which were themselves resistant to atropine, had overcome finally, by 1933, Loewi's very proper hesitation; but the same kind of difficulty has reappeared more recently in a somewhat new form in relation to both parasympathetic and sympathetic transmission. Henderson and Roepke (1934) observed that stimulation of the parasympathetic pelvic nerve produced on the urinary bladder an effect in two phases, a contractile and tonus phase. Acetylcholine, unless injected in sufficient concentration to stimulate the autonomic ganglion cells, reproduced only the tonus phase of this effect, and only this phase was susceptible to atropine paralysis. Bacq and Monnier (1935) report an effect in many ways similar, produced by the synthetic dioxane derivative, numbered 933 F, on the response of the nictitating membrane to sympathetic impulses. Here, again, stimulation of the cervical sympathetic nerve causes an initial quick retraction of the membrane, followed by a secondary, slow phase. Only the latter is reproduced by injecting adrenaline, and this phase alone is weakened or suppressed by 933 F, leaving the initial, quick response to nerve stimulation relatively unaffected, or even enhanced.

Bacq and Monnier, and, if I understand them correctly, Henderson and Roepke, regard the first, quick phase of these reactions as due to the direct passage of the propagated physico-chemical disturbances, which constitute the nerve impulses, to the particular plain muscle fibres on

which the nerve fibres end directly. They regard this as being, for plain muscle under normal conditions, a subsidiary mechanism, the transmission of excitation from nerve endings to such muscle being still mainly effected by release of the chemical transmitter. If we accept this conception, I suppose we should regard the chemical transmission of excitation from nerve ending to effector cell as the more primitive or archaic process. From the observations of Pouchet (1876), of Hogben (1922, 1923, 1931) and especially of G. H. Parker (1936), we have learned that the expansion and contraction of chromatophores, in the skin of lower vertebrates, may be controlled by autonomic nerve impulses in some classes, as in the fishes, and again in the reptiles, while in the amphibia the control may be effected by hormones from distant endocrine organs. Where control is by the nerves, these may have their endings in close relation to the contractile chromatophore cells, or at a significant distance from them. Whether the control is by nerves or from endocrine glands, the evidence suggests that here the immediate, effective stimulus is chemical. Passing to the involuntary muscle and gland cells, we find an autonomic nerve supply, the effects of which are, chiefly at least, transmitted by the release at the nerve endings of one or the other of two chemical stimulants, acetylcholine and epinephrine; to use a terminology which I introduced, we have a nerve supply of which the fibres are cholinergic or adrenergic; and the effects of the adrenergic fibres are curiously reinforced or duplicated by the distribution of epinephrine as a true hormone, carried in the blood from the suprarenal medulla. But Bacq and Monnier would have it that this system of chemical transmission is already supplemented, in certain tracts of plain muscle, by the intervention of a still subsidiary mechanism of physical transmission, concerned with the evocation of a quicker type of contractile reaction. This direct physical transmission is destined, on this conception, to become the predominant or exclusive method for the quick, individualized transfer or excitation at interneuronal synapses, or at the motor nerve endings on voluntary muscle fibres.

There is, however, another way of looking at the same experimental facts. We may suppose, as before, that the primitive form of neuromuscular transmission is one in which a chemical stimulant, liberated at a free nerve ending, reaches the effector cell slowly, by diffusion from a significant distance; and that the need for an increasing speed and localization of reaction is met by a concentration of the same process, due to an increasingly intimate relation of the nerve ending to the effector cell. Ultimately we may suppose that the transmitter comes to be liberated in relatively high concentration, in immediate relation to those plain muscle cells on which the nerve fibres directly end; that its abrupt appearance there produces a quick reaction, starting from these directly innervated cells; and that, in addition, it diffuses from the site of its liberation to reach other, not directly innervated cells, producing in them a secondary, slower reaction, similar in every way to that which the transmitter will produce when it is given by artificial injection, and reaches the effector cells by slow diffusion from the blood. On those lines I think we could account for the two-phase reactions described by Henderson and Roepke and by Bacq and Monnier, and the resemblance of the second phases of these to the effects of acetylcholine or epinephrine given by artificial injection, without postulating the intrusion of a new, purely physical transmission of excitation from nerve to muscle.

How are we to judge between these rival interpretations? They would, I think, account equally well for the facts so far considered. You will note, however, that Bacq and Monnier's interpretation implies the assumption that, in the physical transmission, invoked by them to account for certain relatively quick responses of plain muscle, we see the emergence of the process which is to become all-sufficient for the voluntary striated muscles. The alternative conception raises, on the other hand, the question whether even for these, with their quickly and individually reacting fibres, the neuromuscular transmission of excitation may not be effected by a sufficiently sudden and concentrated

release of a chemical transmitter at the motor nerve ending, in immediate relation to the nucleated end plate of the striated muscle fibre. Our choice between these two conceptions will depend, accordingly, on our readiness to admit the possibility of an essentially chemical transmission, even from motor nerve to voluntary muscle. Four years ago Otto Loewi was not ready for this admission. "Personally," he said, "I do not believe in a humoral mechanism existing in the case of striated muscle." Almost exactly a year later, W. Feldberg and I (1934) made a first preliminary communication of evidence which had led us to believe that such a mechanism nevertheless existed.

For the starting-point of this new development I must ask you to look back for a moment to the description which I had given, in 1914, of the action of acetylcholine. All those actions in which it reproduced the peripheral effects of parasympathetic nerves were easily abolished by atropine; for brevity I had referred to them collectively as "muscarine" actions. When atropine had thus eliminated these, another set of effects came to light, requiring rather larger doses of acetylcholine to elicit them, and closely similar in their nature and distribution to the effects of nicotine. The effects included an intense stimulation of the cells of all autonomic ganglia, and, as later appeared, of voluntary muscle fibres. It was astonishing, indeed, to find these structures stimulated by the same substance as, in the absence of atropine, had so closely reproduced the peripheral, parasympathetic effects. Frankly puzzled, I could at that time only suggest some vague kind of "biochemical similarity between the ganglion cells of the whole involuntary system and the terminations of voluntary nerve-fibres in striated muscle, on the one hand, and the mechanism connected with the peripheral termination of cranio-sacral involuntary nerves on the other." But, if this duplex activity of acetylcholine was puzzling in 1914, what were we to say of it in 1933 when, after an accumulation and sifting of evidence over many years, all concerned, including Otto Loewi himself, were ready to recognize

acetylcholine as the actual substance released to transmit the peripheral effects of parasympathetic nerves, and of some exceptional nerve fibres belonging to the true sympathetic system? Its "muscarine" actions were thus related to a truly physiological function. What, then, could be the significance of its "nicotine" actions on ganglion cells and voluntary muscles? Were these without physiological meaning?

There were many reasons for hesitation in suggesting that acetylcholine might act as the transmitter of excitation at ganglionic synapses or at voluntary motor nerve endings. The transmission at those points had, equally in both cases, the appearance of a direct, unbroken conduction. In each case a single impulse, reaching a ganglionic synapse or a motor nerve ending, caused the passage, from a ganglion cell along a postganglionic nerve fibre, or from a motor end plate along a voluntary muscle fibre, of a single corresponding wave of excitation. If acetylcholine were here to intervene, as the direct stimulator of the ganglion cell or the muscle end plate, it could only do so by appearing with a flash-like suddenness, from some depôt holding it in inactive association, when a nerve impulse reached a preganglionic or motor nerve ending; and, having produced its stimulating effect and started a secondary wave of excitation from the ganglion cell or the muscle end plate, it must then disappear with a comparable rapidity, in the brief span of the refractory period. The only mechanism which we could picture, by which such a rapid removal of acetylcholine from the site of its release could be effected, was a local concentration, on surfaces at the nerve endings, of the specific cholinesterase, which is generally distributed in the tissues, and which, even in dilute solution, so rapidly inactivates acetylcholine by hydrolysis. I may note, in passing, that recent experiments by Brown and Feldberg (1937) and by Brücke (1937) in my laboratory have shown that the relatively large amounts of acetylcholine and of cholinesterase, which can be artificially extracted from a normal sympathetic ganglion, do, in fact, largely disappear when the preganglionic fibres are cut

and allowed to degenerate. Marnay and Nachmansohn (1937) have still more recently obtained evidence of a local concentration of cholinesterase at the neural region of the frog's sartorius.

Our direct evidence of the participation of acetylcholine in the transmission of these rapid excitatory effects came first in the case of the ganglion. Chang and Gaddum (1933), confirming Witanowski, had found in my laboratory that sympathetic ganglia gave a surprisingly large yield of acetylcholine to extraction. Then Feldberg, Minz and Tsudzimura (1934) observed that, when the splanchnic nerve was stimulated, acetylcholine appeared at its endings in the suprarenal medulla, there to act as the direct stimulus to the output of epinephrine into the blood. The medullary cells are morphologically analogous to sympathetic ganglion cells, and Feldberg found that the action of acetylcholine on them belonged to the "nicotine" aspect of its action. Obviously we had to see whether stimulation of preganglionic fibres would cause acetylcholine to appear in the ganglion; and Kibjakow (1933) had described a suitable perfusion technique, just when it was required. Using this, with the modification that they added eserine in very low concentration to the perfusion fluid, Feldberg and Gaddum (1934) had no difficulty in proving that, whenever the preganglionic nerve was stimulated, but only then, acetylcholine appeared in the fluid which issued from the vein of the ganglion. It appeared, indeed, in such concentrations that this venous fluid, on reinjection into the arterial side of the perfusion would, on occasion, produce an output of impulses from the ganglion cells. If the liberation of this acetylcholine, appearing thus diluted in the total effluent, took place at the synapses, its appearance there could not fail to stimulate the ganglion cells. Feldberg and Vartiainen (1934) tried the effects of sending impulses through the ganglion of the vagus trunk, where they encounter no synaptic interruptions, and of firing impulses from the postganglionic nerves back into the cells of the sympathetic ganglion, where they stop without

passing the synapses. They obtained no trace of acetylcholine in either case, though preganglionic stimulation in the same experiment caused its immediate appearance. The phenomenon was so regular that they could calculate the amount of acetylcholine liberated at the synapses by a single preganglionic volley, and therefrom the quantity liberated by one impulse in contact with one ganglion cell; it was of the order of 10^{-15} gramme, or about 3 million molecules of acetylcholine. They further observed that the ganglion cells could be paralyzed by nicotine and curarine, and that, under these conditions, preganglionic stimulation still caused the appearance of acetylcholine, though neither this stimulation, nor the injection of acetylcholine into the artery of the ganglion, now had any effect on the ganglion cells. Brown and Feldberg (1936a) later found that an appropriate dose of curarine, while it abolishes simultaneously the reactions of the ganglion cells to preganglionic nerve impulses and to acetylcholine, leaves them fully responsive to potassium ions. We are inevitably reminded of the observations of Loewi and Navratil (1924) on the effect of atropine on the frog's heart.

These observations have seemed to us to lead inevitably to the conclusion that, in spite of the considerations which made the idea initially difficult to entertain, the excitatory process is actually transmitted across a synapse in an autonomic ganglion, by the liberation of acetylcholine as the impulse reaches the endings of the preganglionic nerve fibres. With regard to the mechanism by which acetylcholine is thus liberated from the inactivating and protective complex in which we must suppose it to be held in the neighbourhood of the preganglionic nerve ending, Brown and Feldberg (1936b) have made the very suggestive observation that, if the potassium content of the perfusion fluid is suddenly augmented, acetylcholine promptly appears in the venous effluent from the perfused ganglion, in a manner strongly reminiscent of its appearance when the preganglionic nerve is stimulated. There is evidence connecting the propagated impulse along a nerve fibre with a wave of mobilization of potassium

ions; and it is tempting to picture this process arriving at the ending of the preganglionic fibre, there immediately liberating a small charge of acetylcholine, which causes the discharge, from the nerve cell sensitive to its action, of a new propagated impulse, perhaps a new wave of potassium mobilization, passing along the postganglionic fibre.

It would be wrong to suggest that this conception has proved to be generally acceptable. Eccles (1936), in particular, has subjected it to a frank and resourceful criticism. This is not the occasion for attempting to reply to his arguments in detail. They may fairly be said, I think, to centre round the failure to detect a repetitive discharge of the ganglion cells, in response to a single preganglionic volley, when eserine has been administered. It is true that, when acetylcholine reaches the ganglion cells by slow diffusion from the blood vessels, a peripheral response, best recorded as a retraction of the nictitating membrane, is evoked, which can only be attributed to a repetitive discharge of impulses from the cells of the ganglion. It is reasonable, accordingly, to enquire whether eserine, by depressing the cholinesterase at the synapses, will not allow the acetylcholine, liberated by a single preganglionic volley, to persist there long enough to produce such an effect. I think that it is, in fact, not certain that the potentiation of the effect of preganglionic stimulation, which Feldberg and Vartiainen (1934) observed with a low concentration of eserine was not of this kind. The position, however, is complicated by the fact that persistence of acetylcholine in contact with the ganglion cells very soon produces a depressant effect, in place of a continued stimulation, and that eserine, in concentrations above a certain low level, paralyzes the response of the ganglion cells to preganglionic impulses or acetylcholine, in a manner recalling the effect of nicotine or curare. We can admit that there are still points of difficulty here to be resolved, without regarding them as destroying the significance of all the positive evidence in favour of chemical transmission at the ganglionic synapses, by the sudden

release and disappearance of acetylcholine there, in immediate relation to the ganglion cells.

The case of the voluntary muscle presented additional difficulties. A sympathetic ganglion is a small structure, and the synaptic endings of preganglionic fibres are closely packed in it. If acetylcholine were liberated by the arrival of preganglionic impulses at these endings, we might expect to find it in reasonable concentration, in the fluid slowly percolating through the very small vascular bed of the ganglion; and my colleagues had, in fact, so found it. In the voluntary muscle, on the other hand, the motor nerve endings are thinly scattered, one to each fibre, through a relatively enormous mass, and only a very small part of the perfusion needed to keep the muscle alive makes any contact with them. If acetylcholine were liberated at these endings by the arrival there of motor nerve impulses, we should, accordingly, expect to find it, if at all, only in very low concentration in the fluid flowing rapidly from the vein. The concentration which we found was small, indeed, but not too small to be detected and measured by the delicate physiological tests available. [Dale, Feldberg and Vogt (1936)]. The substance so detected showed the physiological activities of acetylcholine, not only on one test object, but in the characteristic proportions on several, including some reacting to its "nicotine" and others to its "muscarine" effects. It was rapidly destroyed by cholinesterase or by alkali; there could be no reasonable doubt, indeed, as to its identity. Though the quantity obtained was small, it was of the order to be expected. Calculating, as in the case of the ganglion, the quantity liberated in a muscle by a single, maximal motor volley, and then, from the number of muscle fibres, the quantity liberated by one impulse arriving at a single motor nerve ending, we obtain a number of the same order as that obtained for a single impulse impinging on a single ganglion cell, namely 10^{-15} gramme, or about 3 million molecules. I do not lay any stress on the actual value thus calculated from, admittedly, very imperfect data; I quote it only as evidence that the small amount

of acetylcholine obtained, in the case of the voluntary muscle, created technical difficulties of experiment rather than theoretical difficulties of interpretation.

This acetylcholine was obtained when the muscle responded to stimulation of its motor nerve fibres alone, to the complete exclusion of the automatic and sensory fibres found in the mixed muscular nerve. If the muscle, however, was freed from nerve endings by degeneration, and made to contract by direct stimulation, not a trace of acetylcholine appeared. On the other hand, if the response of the muscle to motor nerve impulses was completely suppressed by curarine, stimulation of the nerve caused the usual output of acetylcholine from the quiescent muscle. As in the case of the heart treated with atropine, or the ganglion cells with nicotine, the acetylcholine was not produced by the response of the effector cells, but by the arrival at the nerve endings of the impulses which normally evoked that response.

Before we were entitled, from such evidence, to suggest that this appearance of acetylcholine, in response to a motor nerve impulse, provided the effective stimulus for the quick, propagated contraction of a voluntary muscle fibre, there were other and serious difficulties still to be met. The chief of these was the lack of convincing evidence that acetylcholine was capable of eliciting, from a normal voluntary muscle, a reaction of this type. The known reactions of voluntary muscles to acetylcholine, whether these were the normal muscles of frogs and other lower vertebrates, or the denervated muscles of mammals, appeared to be of the nature of slow contractures, rather than tetanic summations of quick, propagated contractions. As for the normal muscles of mammals, their responses even to large doses of acetylcholine were, at best, doubtful and irregular. When we reflected on the manner in which acetylcholine must reach the end plates of the muscle fibres, if it acted, indeed, as the transmitter of excitation from the motor nerve endings—that it must be liberated quite suddenly, so that its concentration would rise abruptly and simultaneously at every motor end plate,

falling with a comparable speed during the refractory period of the muscle fibre—it was clear that the ordinary methods of administration, by immersion of the excised muscle, or by injection of acetylcholine into the general circulation, could not be expected to reproduce these effects of its natural liberation. We could not imitate them closely by any artificial method of application, but we could, at least, secure a much more rapid access of acetylcholine to the sensitive points, presumably the motor end plates, of the muscle fibres, by suddenly injecting a small dose, dissolved in a small volume of saline solution, into the blood vessels of the muscle, momentarily emptied of blood by clamping the main artery. Even so, only a small part of the dose injected would reach the points of action; it would not reach them simultaneously but, at best, in rapid and irregular succession, and it would continue for a measurable interval to reach each end plate by diffusion. Altogether, if acetylcholine were indeed the transmitter of motor nerve excitation, the best result which we could expect from such an artificial injection of it would be a short burst of irregular tetanus; and this is exactly what we obtained. [Brown, Dale and Feldberg (1936); Brown (1937a)]. A dose as small as 2 γ, given by this close, rapid injection into the empty blood vessels of the muscle, would produce a contraction of the same tension as a maximal motor nerve twitch, and not widely different from it in rapidity or duration, which nevertheless was shown by the electrical record to be a short, asynchronous tetanus. There was no doubt, however, that it was compounded of quick, propagated contractions. It was in no sense a contracture.

More recently my colleague Brown (1937b) has obtained electrical records from the gastrocnemius of the frog, and from the denervated mammalian muscle, showing the nature of the responses of these to small doses of acetylcholine given by the method of sudden, direct injection into their empty blood vessels. To small doses of acetylcholine, such as 1 γ, thus injected in 0.1 c.c., the frog's gastrocnemius responds by a simple, asynchronous tetanus, with a

maximal tension of several hundred grams, and accompanied by a long-lasting outburst of quick potential changes. With larger doses this initial tetanus is easily cut short by the onset of a contracture, which abruptly terminates the electrical outburst. The same sequence of effects is seen when increasing doses of acetylcholine are administered, by close arterial injection to a denervated mammalian muscle. The smallest doses used are of a much lower order than those needed to excite the normal mammalian muscle, but their effects are tetanic contractions. As the dose is increased to the order of 1 γ, the initial tetanic response is cut short by a contracture, with the onset of which the muscle becomes electrically silent. The reactions of the normal frog's muscle accordingly resemble those of the denervated more closely than those of the normal mammalian muscle.

If we were right in our supposition that the rapid removal of acetylcholine, from the site of its liberation at the motor nerve endings, was due to a local concentration there of a cholinesterase, it ought to be possible by means of eserine so to depress the action of this esterase, as to delay the disappearance of the acetylcholine liberated by a single motor nerve volley, and thus to modify the response of the muscle. There was no reason, in this case, to anticipate a paralytic effect of eserine on the muscle fibre, and its effect on the mammalian muscle was, indeed, to convert the single twitch, normally evoked by each single nerve volley, into a short tetanus, with a tension which might be as much as five times that of the normal twitch. Bacq and Brown (1937) have examined a series of synthetic eserine substitutes, and have found that their activities, in thus potentiating the mechanical responses of a mammalian muscle to single nerve volleys, are closely parallel to their depressant actions on cholinesterase, which had been independently determined.

We have noted that acetylcholine, if it persists in contact with a ganglion cell, exercises a secondary depressant action. In spite of the potentiating effect of eserine, which we have just been considering, the same depressant

effect can be traced in the mammalian muscle under eserine, when nerve volleys follow in too rapid succession, or when acetylcholine is applied by artificial injection. Bacq and Brown have shown that a period of faradic stimulation of the motor nerve, under such conditions, may leave the muscle for some time irresponsive to further nerve volleys, and that an injecton of acetylcholine will produce a closely similar, curare-like paralysis. There are many points, especially some concerning this secondary, depressant action of acetylcholine, on which further evidence is needed before we can consider their proper relation to the normal physiological process. I hope, however, that the facts which I have brought to your notice have been sufficient to convince you that there is already a case worthy of serious consideration, for the intervention of acetylcholine, in virtue of its nicotine action, as the chemical transmitter of the excitatory process both at ganglionic and at voluntary, neuromuscular synapses. I do not expect, and certainly do not desire, the acceptance of such a conception too easily, or without a thorough and critical scrutiny. I am aware that a certain resistance to it is likely to arise, not merely on its own account, but also from the possibility of its further implications. I know that Dr. Eccles, for example, has made his elaborate studies of the electrical reactions of the sympathetic ganglion, as furnishing an accessible model of the synapses of the central grey matter; and I know from conversation with one whom many of us revere as our master in this field, that Sir Charles Sherrington looks upon the transmission of excitation from a motor nerve ending to a voluntary muscle fibre as probably furnishing a pattern, or paradigm, of what happens at a central synapse.

Such analogies must provoke thought and speculation, but I venture to urge that they have their chief value as a stimulus to the search for direct, experimental evidence. I think I may claim that no definite suggestion was made of a chemical transmission from motor nerve ending to voluntary muscle fibre on mere analogy, or until the experimental evidence seemed to us not only to justify, but

even to require such an interpretation. Similarly, I think that the mechanism of synaptic transmission in the central nervous system ought to be regarded as a matter for separate, direct investigation. Results obtained on a peripheral ganglion or a voluntary muscle may suggest possibilities to be tested, and even methods of investigation. If direct evidence could be produced, in favour of a chemical transmitter at the central synapses, it would require a critical scrutiny in relation to conflicting evidence, which suggests a purely physical mechanism; and if the evidence for a chemical transmitter prevailed, we should need further direct evidence, before we could identify it with one of those which have been found in the peripheral nervous system. An understanding of the process by which nervous excitation passes from neurone to neurone in the measureless complexity of the central grey matter, must surely be one of the highest aims of investigation, the attainment of which would have a transcendent importance, for physiology and for practical medicine. It is the more necessary, I think, that every step towards that goal should be firmly based on experimental data. Nearly three hundred years ago the principle which should guide us was laid down by the founder of experimental medicine, from whom this Society takes its name:—

"Nature is herself to be addressed; the paths she shows us are to be boldly trodden; for thus, and whilst we consult our proper senses, from inferior advancing to superior levels, shall we penetrate at length into the heart of her mystery."

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CHEMICAL WARFARE AS DEVELOPED DURING THE WORLD WAR AND PROBABLE FUTURE DEVELOPMENT*

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INTRODUCTION

I shall attempt to present for your consideration those salient facts concerning chemical warfare which are of special importance to the medical profession. I hold no exaggerated conception that chemical warfare will dominate the battlefields of the next war. The infantryman supported by the other Arms and Services is still, in so far as we can now tell, the spear point and the foundation element of both attack and defense. However, all military experts agree that chemical warfare will be an extremely important weapon in a future war; that it will tend to modify strategy and tactics; and that no military plan should be made without giving careful consideration to this new weapon.

A reasonable estimate based upon World War experience and chemical warfare developments since the war is that a very high percentage of future casualties will be from the chemical weapon. Hence the particular importance of this subject to medical men.

While avoiding the temptation to let the imagination soar and a possible tendency to exaggerate the importance of chemical warfare, we may reasonably join with the British soldier and scientist, Victor Lefebure, in the statement, "That the only new casualty producers, the real aggressive agents which have developed since the Middle Ages are chemicals. . . . Other branches have contributed towards improving, and have, in fact, revolutionized certain weapons. But chemical science is the only one which has introduced new casualty producers. . . . It is a solid fact that although we may employ this term

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in a general way yet today the new agencies of war center around chemistry."

The often repeated statement that the next war will begin, as to means and methods, where the last war left off cannot be safely accepted as an axiom. This is particularly true as to chemical warfare. To predict correctly the course and character of a future war is most difficult and probably beyond the power of our wisest and most experienced military men, but to attempt this prediction is absolutely necessary if we are to direct our military medical preparation along sound lines. It is reasonable for us to start from what we know of the World War. We do know that, although the Germans had expended a large portion of their chemical munitions before we entered the war, gas caused twenty-seven per cent of our A.E.F. casualties. It had grown more and more important as a tactical weapon with the progress of the war. The aeroplane was in its initial stages of development during the World War, and there were no aero-chemical attacks except the use of incendiary bombs. The possible means and methods of using gas as a weapon in a future war have been so greatly extended by the improvement of the aeroplane and other technical developments that it is reasonable to assume that in a future war the number of casualties from aero-chemical attack will be tremendously greater than the gas casualties of the World War. The burden on the Medical Corps will be correspondingly increased. At this point it is essential to emphasize that by a casualty is meant a soldier incapacitated for fighting, not necessarily a death, nor even a seriously wounded man. With modern means of chemical protection there will be relatively few deaths or even serious wounds from gas but a multitude of lightly injured who will recover completely within several weeks. It is to be remembered that a wounded man is much more of a handicap to an army than a dead soldier. A dead soldier although lost to the fight requires no rations, needs no further care, while a wounded man on the average absorbs for weeks or months the activities of four attendants as his share of transpor-

tation, supply, hospitalization and other essential facilities. It is also true that, while the Medical Corps cannot do much to prevent casualties when bullets and high explosive shell are launched, it can do much toward preventing soldiers who have been exposed to gas from becoming casualties. Indeed the major portion of this burden of caring for numerous light gas casualties and for preventing gas casualties initially must be borne by the Medical Corps.

Are you, as civilian medical men and potential officers of the Medical Corps prepared to assume this increased burden with the brilliant success which marked your efforts in the World War? Much as I admire your past achievements and your potentialities, I question whether you are now prepared for your part in a war of the future in which chemicals will be largely used. Your peacetime training tended to prepare you for your World War duties where gas was not a dominant factor. The more extensive use of gas in a future war introduces medical problems for the solution of which your experience in civil life does not furnish adequate preparation. Have you given due consideration to what chemical warfare will mean to the medical profession in a future war? Have you directed your thought and training toward working out means and methods of handling efficiently the tremendous number of gassed patients who will tend to clog first aid, evacuation and base hospital facilities? Are we lagging behind the armies of the rest of the world in the preparation for this eventuality? These are questions vitally important to our national defense. It is true that the continuous threat of war in Europe spurs on their medical men to prepare for the day and that we lack this incentive to prepare. We, however, must not be lulled to a false sense of security by the blessings of our distance from the scenes of foreign strife nor by our ocean moats.

Immediately before the World War the science of chemistry and chemical industry had made great strides. One of the major participants in the war, Germany, led the

world in chemical science and in industry based on that science. After the Battle of the Marne there was a deadlock on the Western Front. Both sides were dug in, with approach to their underground shelters protected by barbed wire. Later on reinforced concrete was added. One flank was secured by Switzerland and the other by the sea. Maneuver was out of the question. The available technical and tactical resources of the soldier could not solve the problem. Strategy in so far as the Western Front was concerned had exhausted its possibilities. Professor Haber, dean of German scientists and head of the famous Kaiser Wilhelm Institute came to the rescue of Germany.

It is a fact of great historical and scientific importance that Professor Haber and chemical science had already saved Germany from certain defeat. A form of chemical warfare of far greater importance than gas warfare had already been put in operation in Germany by reason of Haber's knowledge and skill. War cannot be carried on without military explosives. Military explosives cannot be made without nitrogen. Before the World War the only known commercial source of nitrogen for explosives was the nitrate fields of Chile. With but a few months supply of nitrates on hand Germany in 1914 was cut off by the Allied Fleet from this source. Unless some other source of nitrates were made available, Germany would be inevitably compelled to capitulate. Haber invented and put into operation his process for the fixation of nitrogen from the air. Germany was thus saved by a chemist from certain defeat at this early stage.

Now, once more, Haber came forward and proposed a means for breaking the deadlock on the Western Front. It was to bombard the Allies not with high explosive shell but with molecules, which would sink into dugouts and trenches, shoot around corners and reach an enemy where the heaviest shells would be ineffective. From the huge forty-two centimeter howitzers which had been so effective against Liege and Namur, he descended to the infinitesimally small, i.e., to molecules of chlorine gas. It may be noted that he selected a chemical which would not only be

effective on the battlefield but which was widely used in industry and was therefore commercially available in quantity.

Professor Haber by considerable effort persuaded the conservative German General Staff to allow him to try gas as a weapon against the Allies to break the deadlock. The General Staff, however, being occupied with preparations for the Tarnow-Gorlice breakthrough on the Eastern Front and uncertain as to the probable success of the gas attack, furnished second class troops and inadequate reserves and thus missed an opportunity of breaking through the Allied lines to the sea and of exploiting this breakthrough to achieve a decisive victory.

Several thousand cylinders of this common industrial gas, chlorine, were installed in the trenches on a four mile front north of Ypres. At five o'clock in the evening of April twenty-second, 1915, when the wind was right, these cylinders were opened and a cloud of chlorine gas drifted down over the two French Divisions in that part of the line. The Allied troops being without protection, either fled or were overcome. The German troops penetrated unopposed on a four mile front to a depth of three and a half miles into the Ypres Salient and then at seven thirty p.m., with their second class attacking troops mixed up and demoralized and without adequate reserves to give a forward impulse, the German troops settled down and entrenched. The Allies in their turn were so demoralized that they were unable to make the first counter attack until after midnight, seven hours after the German jump-off. But the Germans through lack of initiative, imagination and foresight had lost the golden opportunity. Thereafter throughout the war each side mobilized its chemists and industrial and military technicians to seek for effective war chemicals, means and methods of using them on the battlefield and means and methods of chemical protection.

For convenience in discussing the chemical agents used during the war it may be well to give you the system of

classification used by the Chemical Warfare Service. Chemical agents may be classified as follows:

(1) Physiological effect:
  (a) Lung irritants (CL) (CG)
  (b) Vesicants (HS) (Ml)
  (c) Lacrimators (PS) (CA)
  (d) Irritant smokes (DA) (sternutators)
  (e) Nerve and blood poisons (hydrocyanic acid)
  (f) Others (physiological action incidental)
    (1) Screening smokes (WP)
    (2) Incendiaries (WP) (thermit) (oils)

(2) Tactical employment:
  (a) Screening
  (b) Harassing (lacrimators, irritant smokes and sternutators)
  (c) Casualty (vesicants and lung irritants, plus white phosphorus)
  (d) Incendiary

(3) Explanation of abbreviations:
  CL=CHLORINE
  CG=PHOSGENE
  HS=MUSTARD GAS
  Ml=LEWISITE
  PS=CHLORPICRIN
  CA=BROMBENZYLCYANIDE
  DA=DIPHENYLCHLORARSINE

After investigating possibly a thousand chemicals which gave promise of being suitable for use in war, about a score were actually tested on the battlefield. Of these latter the following proved to have important tactical value.

(1) CHLORINE

Chemical name—Chlorine (Cl_2).

Physiological classification—lung irritant.

Physiological action—burns upper respiratory tracts.

Historical Sketch. Chlorine first used in war by the Germans against Allied troops at Ypres, Belgium, April 22, 1915.

(2) PHOSGENE

Chemical name— Carbonyl chloride ($COCl_2$).

Physiological classification—lung irritant.

Physiological action—causes edema.

Historical Sketch. CG was first made by John Davy, English chemist, in 1812, by reaction of CO with Cl in presence of sunlight. Made with bone charcoal as a catalyst in 1915.

CG was first used in war by the Germans against British troops in December, 1915, in cloud gas attacks mixed with chlorine.

(3) CHLORPICRIN (VOMITING GAS)

Chemical name — Trichlornitromethane (Cl_3CNO_2).

Physiological classification—lacrimator and lung irritant.

Physiological action—lacrimates, irritates nose and throat, produces nausea and lung irritation in order as concentration increases.

Historical Sketch. Chlorpicrin was first prepared by the English chemist, Stenhouse, in 1848, by the reaction of bleaching powder and picric acid; also prepared by reaction of chloroform with nitric acid.

PS was first used by the Germans against Italians in spring of 1917, on the Western Front.

(4) TEAR GAS

Chemical name—Brombenzylcyanide ($C_6H_5CHBrCN$)

Physiological classification—lacrimator.

Physiological action—causes severe lacrimation and nose irritation, temporary only.

Historical Sketch. This gas was used by French during World War as tear gas loaded in artillery shells.

(5) MUSTARD GAS (the most important of all war gases)

Chemical name—B^1 dichlorethyl sulphide ($ClCh_2$-$CH_2)_2S$.

Physiological classification—vesicant, blistering.

Physiological action—dissolves in skin or lung tissue, then produces burns.

Historical Sketch. Mustard gas was first carefully investigated by the German chemist Victor Meyer, in 1886. It has been prepared and described by the English chemist, Guthrie, in 1860.

(6) ETHYLDICHLORARSINE

Chemical name—Ethyldichlorarsine ($C_2H_5AsCl_2$).

Physiological classification—vesicant and sternutator.

Physiological action—vesicant; one-sixth as powerful as HS. A powerful sternutator.

Historical Sketch. The Germans used this material as a filler for yellow cross No. 1 and green cross No. 3 shells during World War; 1,092 tons were made at Hochst and filled into these two munitions.

(7) SNEEZE GAS. (DIPHENYLCHLORARSINE)

Chemical name — Diphenylchlorarsine C_6H_5ASCl C_6H_5)

Physiological classification—sternutator; irritant smoke.

Physiological action—sneezing, vomiting, headache.

Historical Sketch. Introduced into war by Germans in 1917. Several hundred thousand shells with this filling were fired against allies. Small bottle of gas in HE shell was used. Harassing effect of sneeze gas as well as effect of HE shell thus obtained. No deaths and relatively few serious injuries resulted from the World War use. It is particularly suited for temporarily incapacitating an enemy without doing him serious or permanent injury. This is the agent with which writers of horror tales wiped out the population of New York City.

(8) WHITE PHOSPHORUS

Chemical name—White Phosphorus (P_4) (Yellow Phosphorus).

Physiological classification—none.

Physiological action—solid particle burns flesh; smoke relatively harmless.

Historical Sketch. WP is a casualty agent, an incendiary and a smoke producer. WP used during World War as a filling for 4" S.M. shells by British. One thousand and six tons of WP made in United States during World War; 190 tons shipped overseas.

(9) Thermite

An incendiary consisting of a mixture of iron oxide and aluminum. Used largely as a shell filler and in aviation bombs.

Weapons Used to Protect Chemical Warfare Agents in the World War

(1) Cylinders of the type used in commercial life were first used. When opened the gas drifted with the wind as a cloud of vapor. This is a cumbersome and uncertain method and although used off and on to the end of the war was soon in the main superseded by some type of cannon to throw the gas in a container well into the enemy lines so as not to be dependent upon the wind.

(2) The four inch Stokes mortar and the crude but effective Livens projectors were developed by the British to throw gas projectiles into the enemy lines. These cheap, crude weapons were eventually adopted by all armies.

(3) Gas in artillery shell was, however, by far the most important method of placing gas within an area occupied by an enemy. Most of the gas attacks were made by artillery fire.

(4) No chemical agents except incendiaries were put down by aircraft.

Protection Against Chemical Warfare

General:

"Protection is an essential factor in war. For the individual the demand for protection springs from the fundamental instinct of self-preservation. Man clings to life and seeks both instinctively and deliberately to protect himself to the last, even though he may, as he often does,

welcome great danger. It is the universality of this urge for life that makes acts of great individual sacrifice and heroism exceptional and causes them to be singled out and rewarded. In consequence of this the history of war might well be viewed as an age-long and continuing struggle between weapon development, or the means of taking life, on the one hand; and protection, or measures for safeguarding life, on the other."

"The shield may be considered as the beginning of body armour, the development of which reached its zenith in the complete suit of mail of the medieval armoured knight. But with the Battle of Crecy in 1346 this form of individual protection received a definite check. The ultimate adoption of gunpowder for war purposes hastened the end. With the advent of breach-loading firearms, emphasizing greatly the need for mobility and open formations, individual armour passed out of the war picture.

"Just as archery and firearms eliminated individual armour, so now is gas changing our ideas of the protective value of simple cover. Chemical warfare is indeed forcing material compromises in hitherto accepted rules of protection. Indeed places of natural cover against missle weapons are often those where chemical agents are most effective." In place of the metal armor protecting against cutting and thrusting weapons and projectiles, soldiers of the future must wear an armor of cloth impregnated with chemicals to neutralize the molecules of gas which threaten the body.

Individual Protection:

The fundamental item of equipment in protection against chemical warfare is the gas mask. Each contending nation developed during the World War a gas mask that protected face and lungs against the chemical agents then used. Each nation since the war has conducted research toward perfecting its mask to protect against all potential war chemicals. The principle of surprise has particularly important application here. A nation having in secret reserve a chemical agent that would penetrate

an enemy's mask but not its own, would have an overwhelming tactical advantage. As I shall show later such a discovery would be very difficult but not wholly impossible.

The results of research on agents and on improvements, particularly in the gas mask canister, are quite naturally carefully guarded secrets of the nation concerned.

The question of a reserve of gas masks not only for its army but also for its civil population is a problem given considerable attention in each European country.

The gas mask protects only the respiratory organs, the eyes and face. For the full protection of the body against the blistering action of vesicant agents, which, either in liquid or vapor form, will readily penetrate ordinary cloth, specially protective clothing is required. Such clothing, including protective gloves and shoes, will probably be issued in time of war by all armies. Impervious protective clothing which did not allow the passage of air but encased the body in an air tight compartment had a very limited use in the World War for troops who were to remain relatively inactive in a mustardized area or who were to wear the clothing for a limited period while demustardizing an area. For active troops, such as Infantry, impervious clothing is impracticable. Each nation is now seeking to develop a chemical with which uniform cloth may be impregnated allowing air to pass through, but filtering out the gas. The advantages of such a means of protection are obvious. It is probable that all armies in the future will be equipped with uniforms protecting against mustard gas while at the same time allowing the free circulation of air through the pores of the cloth.

Collective Protection:

Besides the means of individual protection measures must be taken to protect a group or a number of persons or animals against chemical warfare. In the World War we provided our soldiers with so called gas proof dugouts. The protection was in general inadequate. The probability of the more extensive use of gas in a future war has caused all nations to develop plans for the following:

(a) Gas proof shelters, not only for soldiers but for the population.
(b) Methods of removing gas from enclosed spaces.
(c) Method of decontaminating grounds, buildings, clothing.
(d) Protection of weapons and ammunition against mustard gas.
(e) Protection of food and water.
(f) Warnings of chemical attacks.
(g) Means and methods of first aid and hospitalization.

One can readily see that there are some important and difficult problems here presented. The last one is of particular importance to the medical officer as well as to the civilian practitioner but all are of vital concern to the medical profession.

Gas Casualties in the A.E.F.:

A study of the casualties suffered by the American Expeditionary Forces may be made by examining the official report of the Surgeon General of the Army for the year 1920. According to this report, 258,338 men were wounded by war weapons. Of this number, 34,249 or 13.3 per cent, were killed outright or died on the field before they could be removed. The remainder, 224,089 wounded men, were removed to hospitals for treatment. Of the 70,552 gas casualties, only 1,221, or 1.73 per cent, died. Of the 153,537 admitted to the hospitals suffering from bullet wounds, shell wounds, and all other methods of warfare except gas, 12,470, or 8.12 per cent, died. Taking those that died from gas on the field of battle, estimated at possibly 200, and adding the 1,221 who died in the hospitals, there were 1,441 deaths in France from the effects of gas, which, considering the 70,552 hospital casualties produced by gas, shows that barely two per cent of the gassed cases died.

Of the remaining casualties, 187,586 who suffered from wounds other than gas, 46,519 or 24.8 per cent died, thus showing that the men who were injured by gas alone on the field of battle had in the American Army twelve times as many chances of recovery as those wounded with bullets, high explosives or other means. This figure for our Army

is slightly better than the British, due, no doubt, to the fact that the British Army experienced the gas attacks before devices for gas protection were devised.

The ratio for the German Army was much more favorable to gas, i.e., one to fifteen. This may have been due to a much higher state of gas discipline in the German Army. The more efficient the gas discipline and training the fewer the fatal casualties from gas. Defects in A.E.F. gas discipline produced numerous unnecessary casualties.

Does Gas Produce After Effects?:

After noting how favorable the mortality statistics are for gas, many will raise the question of the dire after effects, blindness, tuberculosis and other lingering ailments. What is the use of having your life preserved if you are permanently disabled or a confirmed invalid? Such are the results of the horror literature, propaganda and failure to look at the facts objectively that the public at large does not know that gas produced relatively few after effects, while bullets and high explosive have dotted the landscape with pitiful derelicts.

BLINDNESS DUE TO WEAPONS OTHER THAN GAS IN THE A.E.F.

Nature of disability	*Rifle*	*Shell*	*Shrapnel*	*Hand Grenades*	*Gun Shot Miscellaneous*	*Others*	*Total*
Loss of right eye	13	40	89	6	64	6	218
Loss of sight of right eye	10	24	17	5	23	10	89
Loss of left eye	19	43	72	7	77	5	223
Loss of sight of left eye	6	14	27	—	17	2	66
Loss of both eyes	3	6	4	1	—	—	14
Loss of sight of both eyes	1	16	6	1	4	2	30
Loss of eye, side unknown	1	12	8	—	7	—	28
Loss of sight, side unknown	3	9	10	—	8	1	31
Loss of sight, due to other conditions	5	22	21	6	19	7	80
TOTAL	61	186	254	26	219	33	779
Blindness due to gas (4 per cent)							33
Blindness due to weapons other than gas (96 per cent)							779
TOTAL CASES OF BLINDNESS							812

BLINDNESS DUE TO GAS

Nature of disability	*Kind of Gas*		
	Unknown	*Mustard*	*Total*
Loss of right eye	2	2	4
Loss of sight of right eye	7	5	12
Loss of sight of left eye	8	2	10
Loss of sight of both eyes	3	1	4
Loss of sight one eye, unknown	2	—	2
Loss of eye, side unknown	—	1	1
TOTAL	22	11	33

Does Gas Predispose to Tuberculosis?:

Certainly if there is one error widespread and deep-seated, it is that gas causes or predisposes to tuberculosis. It seems so natural to the layman that it should cause tuberculosis, that to eradicate this wrong belief is very difficult. It is a common belief on the part of the public that tuberculosis is a necessary consequence of gas poisoning. This matter came before a select committee of the United States Senate on investigation of the United States Veterans' Bureau in 1924. Dr. A. P. Franchine, whose testimony can not be ignored, was, previous to the war, associate professor of medicine at the University of Pennsylvania, where he taught largely on tuberculosis wards and from tuberculosis cases. For fifteen years he was visiting physician to the department of tuberculosis of the Philadelphia Hospital and on the staff of the Phipps Institute for the study and treatment of tuberculosis, and chief of the State tuberculosis clinic in Philadelphia from its foundation in 1907. Doctor Franchine went to France as division tuberculosis specialist, at first attached to the Twenty-seventh Division, and later as consultant in gas to the Fourth Army Corps, where he was not only in touch with administrative and executive work in gas but assigned as chief of the staff at a gas hospital, a 1,000-bed hospital. Doctor Franchine, before the Senate committee, stated:

"The percentage of deaths from gas was less than two per cent. And I went to the post-mortem room every day and examined the lungs. I was not so interested in the effects of gas elsewhere, after I once knew it, but I examined the

lungs to see whether there were latent tuberculosis lesions; that is, lesions that do not give symptoms, such as any of us here may have, and whether there was any evidence of these lesions, pathologically, having been lit up by this more or less intensive inflammation. I do not mean at the time of the gassing but I mean following gassing, when one could expect it. While we were being rushed—and too rushed—to keep records, I suppose I can say that I saw then 100 to 125 posts. In a number of these cases it was perfectly and palpably evident to a man of pathological training that there were healed, nonactive lesions, which is not an uncommon occurrence, as you know. It is considered that probably sixty to ninety per cent of people have at one time or another had a tuberculosis infection. But these palpable latent lesions showed no evidence of activity, or reactivation, from four to six to ten weeks after the acute inflammation which is supposed to give rise to tuberculosis." The consensus of medical opinion among those who have investigated the subject both here and abroad, is that gas has left no large aftermath of cases of tuberculosis among soldiers gassed in the war, nor are gassed cases in general predisposed to tuberculosis.

Chemical Warfare Development Since The World War

The principal of Surprise is of vital importance in chemical warfare. Each nation is carrying on research to anticipate any possible discovery by another nation of a chemical agent that will penetrate the present gas mask canister or otherwise overcome present means of gas defense. Such a discovery would tend to give victory to the nation making the discovery. Each nation is keeping secret the results of its research. We do not know, therefore, whether new and more powerful chemical warfare agents have been discovered since the World War. We do believe that the highly imaginative articles in current periodicals as to new discoveries and their effects are absolutely without foundation. It is probable that no chemical warfare agent more effective

for war use than mustard gas has been discovered since the World War. What we shall face in the next war, as I view it, is a far more extensive use of mustard gas than we experienced in the World War. This will mean tremendously increased burdens for the Medical Corps. The process of manufacturing mustard gas has been greatly simplified and cheapened. Vastly more of this chemical will be available for use than could be manufactured in the World War, and therefore we should concentrate on a defense against the extensive use of mustard gas in a future conflict.

Incendiaries:

White Phosphorus and Thermite were the incendiaries used during the World War. No important new incendiaries have been developed since the World War. A more extensive use of incendiaries will probably characterize a future war.

Smoke candles or smoke boxes had a limited use in the World War. A new and more efficient smoke mixture than that used during the World War has been developed. It is called the H C mixture; chemical name, Hexachlorethane ($C_2 Cl_6$) and Zinc Oxide (ZnO). Liquid smoke materials for airplane smoke screens have been developed since the World War. Probably the cheapest and most effective consists of a mixture of Sulphur Trioxide (SO_3) about fifty-five per cent and Chlorsulphonic Acid ($HCl\ So_3$) about forty-five per cent.

Aero-chemical Attack:

The principal post war development affecting the technique and tactics of chemical warfare is the development of the airplane and of the methods of aero-chemical attack. These constitute far reaching and revolutionary changes. By means of the airplane no part of the enemy territory will be out of range of aero-chemical attack. The great development in putting down chemicals is by sprinkling or sprayng the same from aircraft, thus covering large bodies of troops or extensive areas in a short period of time and at any place in an enemy country. Mustard gas or irritating liquids

such as tear gas or irritant smoke will also probably be used to deny an area to an enemy by sprinkling the ground or surroundings using for this purpose sprinkling carts, military tanks or gas mines.

The probability of the discovery of new and more destructive chemical agents for warfare is remote. The requisites of a chemical warfare agent are so exacting as to limit the field greatly. Laymen have a natural tendency to regard any potent toxic or irritating chemical as suitable for war use. The facts belie this as evidenced for example by hydrocyanic acid, deadly in the laboratory but not usable on the battlefield, as proven by most extensive tests by the French Army. When you have noted the exacting minimum requirements for chemical warfare agents, it will be apparent why the field is very limited.

Exacting Requirements for a Chemical Warfare Agent:

A substance, to be useful as a chemical agent, must have all of the following properties:

(1) It must be very toxic; or very irritant; or produce a large volume of smoke; or have incendiary properties.

(2) It must be stable in storage and reasonably stable in contact with moisture.

(3) It must be capable of manufacture on a large scale.

(4) Raw materials must be available in the continental United States.

(5) It must be suitable for loading in munitions and should have little or no corrosion on ordinary steel.

(6) The substance must be capable of vaporization, or other means of dissemination, in sufficient concentration under field conditions to produce the effect desired.

(7) If the substance is a gas under ordinary conditions, it must be easily compressed to a liquid and easily vaporized when the pressure is released.

In addition to the above absolutely necessary properties, it is highly desirable that a chemical agent possess the following properties:

(1) It should be capable of handling and transportation without special precautions.

(2) When disseminated as a vapor the molecular weight should be several times as great as air.

(3) It should be cheap to manufacture.

(4) It should be capable of quick production in existing commercial plants without extensive alteration in existing equipment.

Is It Practicable to Make Effective the Prohibition of Chemical Warfare? I believe you will concur with the committee appointed by the League of Nations Assembly to consider this question, that the answer is, No.

The committee reported:

a. "Although conventions forbidding the use of gas in time of war might have great moral value, yet no treaty stipulation could certainly prevent secret preparation for chemical warfare. There is only too much reason to fear, after the experience of the late war, that any country fighting for its life will avail itself of whatever weapon it may find it possible to use effectively. It is therefore necessary, however unfortunate it may be, to anticipate if another war breaks out, chemical weapons will be used.

b. "That it is impossible to prohibit or control research which could lead to further discoveries—or to restrict the manufacture of a gas or particular gases."

c. "It is to be feared that chemical weapons will be employed by belligerents to a still greater degree in the future than has been done in the past, for these weapons have shown themselves to be efficacious under circumstances where other arms have been of little or no use."

The United States Is Not A Party to Any Treaty Now In Force or Restricting the Use of Chemicals in War. We have taken part in so many conventions on this subject that even the military mind is confused as to just where the United States stands on this question.

For purposes of clarification the following is quoted from The War Department Manual on Military Law:

"The United States is not a party to any treaty, now in force, that prohibits or restricts the use in warfare of toxic or nontoxic gases, or of smoke or incendiary materials, etc. A treaty signed at Washington, February 6, 1922, on behalf of the United States, the British Empire, France, Italy, and Japan (Malloy, Treaties, Vol. III, p. 3116), contains a provision (art. V) prohibiting "The use in war of asphyxiating, poisonous or other gases, and all analogous liquids, materials, or devices", but that treaty was expressly conditioned to become effective only upon ratification by all of the signatory powers, and, although heretofore ratified by all of the signatories except France, having never been ratified by the latter, has never become effective. The protocol "for the prohibition of the use in war of asphyxiating, poisonous, or other gases, and of bacteriological methods of warfare", signed at Geneva June 17th, 1925, on behalf of the United States and many other powers (League of Nations Official Journal, Aug. 1925, p. 1159), although ratified or adhered to by, and now effective as between, a considerable number of the signatories, has never thus far been ratified by, and is not in force as to, the United States, Japan, and some other powers."

Is It Probable Our Medical Officers will Be Called Upon to Protect Our Army and Civil Population Against Bacteriological Warfare? This is a question that has not only been raised by sensational horror story writers but by far-sighted Medical men both military and civilian. An international commission consisting of Professor Pfeiffer (Breslau), Bordet (Pasteur Institute), Madsen (Copenhagen) and Cannon (Harvard) appointed to investigate this subject, reported to the League of Nations in 1922 essentially as follows.

a. The effects of bacterial injury cannot be limited or localized.

b. Modern water purification methods protect against the organisms of typhoid and cholera.

c. Plague is a disease that would be as dangerous for the force using the organisms as for the attacked.

d. The danger from typhus has been exaggerated.

e. Modern sanitary methods are effective in controlling communicable diseases.

f. Bacterial warfare would have little effect on the actual issue of a contest in view of the protective methods which are available for circumscribing its effects.

g. As regards the poisoning of weapons, the experts point out that the germs which could be employed (streptococci, anthrax spores, glanders bacilli, etc.), would not preserve their danger properties if they were prepared a long time beforehand and allowed to dry on metallic surfaces. Nor if placed in a projectile would these germs better resist the shock of discharge, the rise of temperature and the violence of an explosion which destroys all life. The only method presenting a certain danger would be that of dropping from aeroplanes glass globes filled with germs. The majority of experts are of the opinion that bacteriology cannot at present produce effective substances capable of destroying a country's live stock and crops.

A reasonable conclusion from the report of this Committee of Experts of the League of Nations is that no nation, however ruthless, would probably resort to bacteriological warfare because of the technical difficulties involved and because the danger to its own people would be so great.

Conclusions.

1. There is no practicable way of prohibting or regulating chemical research or the development and manufacture of war chemicals because they are either the chemicals of industry or closely allied thereto.

2. Chemical warfare as evidenced by the World War statistics is the most effective method of using force yet devised by man, with relatively slight destruction of life and property and the minimum of human suffering and after effects. Propaganda and sentimental considerations deny this. An objective study of the facts confirms the truth of the statement.

3. Chemical warfare will be an important weapon in a future war. In the history of warfare no effective weapon once adopted has ever been abandoned until rendered obsolete. Chemical warfare is decidedly effective.

4. The mathematical probabilities are against the discovery of new and more powerful chemical warfare agents. However, continuous research must be carried on as part of an efficient National Defense organization.

Future developments in chemical warfare lie along the lines of more effective use of the agents already known and more effective means of protection against the same.

5. By reason of the abundance of the raw materials required in its manufacture (table salt, water, coal, sulphur and alcohol), the development of the technique of manufacture on a large scale by most countries and the tactical value of the agent, mustard gas will probably be the most important chemical warfare agent in a future war. But the effect on tactics and on the functioning of the Medical Corps will be marked.

6. Mustard gas in the future will produce far more casualties than were produced by any weapon in the World War but they will be light, with few deaths, relatively little suffering and relatively negligible after effects.

7. Until a volatile vesicant is discovered, gas warfare as it stands today and as it will stand in the future, is a more powerful defensive than offensive weapon. This fact arises primarily because mustard gas and similar gases, can be used to make difficult the occupation of or passing over terrain. Hence, it can always be used by a retreating force or by a force on the defensive; whereas, its use by force on the offensive would tend to block the progress of the army using the gas. This does not mean that an attacker would be absolutely precluded from using mustard gas on an enemy area and then attacking through the area. This might well be a sound maneuver particularly if the attacker was well equipped wth protective clothing which the defender lacked.

Care should be taken to avoid absolutes in the discussion of chemical warfare and to deal in relative terms. Mustard gas would be a great obstacle to the landing of troops.

While as now used by aeroplane, artillery, or other weapons, mustard gas is more valuable as a means of defense than of offense, the discovery of a gas of the mustard type but which was volatile and quick acting might readily reverse this situation. We must be prepared mentally and technically for rapid changes in conditions of warfare.

8. The United States is the only country in the world that by reason of its industrial development and natural resources has all the manufacturing capacities and all the raw materials (or substitutes therefore) for carrying on any type of chemical warfare.

9. Our national military policy is solely one of defense for which the chemical weapon is peculiarly suited. The question asked by Dr. Mills, Professor of Chemistry in the University of South Carolina, is pertinent:

"Shall we solemnly set forth that certain chemical compounds shall not be used to defend those that discovered them? Shall we insist that with cheap and effective weapons at hand, the cheap and effective weapons should be discarded and that a more expensive (and, as a matter of fact, more brutal) armament should be maintained?"

10. Armor, not against cutting or thrusting weapons or metal projectiles but against molecules, will characterize troops of the future. Uniform clothing must afford protection against blistering gas while allowing free circulation of air. Any army not so equipped will certainly go down in defeat before an otherwise equal force with protective clothing and means of spraying mustard gas. Troops without protective clothing would find difficulty operating even in tear gas spray, particularly on a hot day.

11. Weapons, tools, etc., sprayed with mustard gas cannot be used until decontaminated. Food and water must be protected from the spray. These present important problems in equipment and training not yet met by our Army.

12. Chemical warfare as evidenced by our World War experience is not a menace to civilization but the contribution of science toward halting the destructiveness of war.

13. Aeroplanes and chemical warfare give to a nation a powerful means of defense in time of emergency without serious expenditure in time of peace. This means national security without large national armaments, thus making for the future peace of the world.

14. The Medical Corps has an important problem not only in caring for gas casualties but in preventing their occurrence. This requires a very considerable training and knowledge not now possessed by the Corps in general.

15. I would emphasize that all which I have previously said seems to lead logically to the conclusion that an otherwise most efficient national defense system may be rendered nugatory without chemical warfare preparation, and as yet we have not made this preparation.

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A REVIEW OF "AMERICAN MEDICINE"

Were we to attempt to characterize in two phrases this remarkable study of the economic phase of the practice of medicine, complete unity of purpose and utter diversity of opinon would perhaps express our primary summation. For he who opens this book with the expectation that he will here find a crystallization of the thought of American Medicine, an evaluation of countless varieties and shades of belief, will be vastly disappointed. The editors at once disclaim any attempt to harmonize so many and so divergent opinions. The reason for this disclaimer is perfectly obvious for it is utterly impractical to derive a creed from so many and so different credos.

The American Foundation Studies in Government, which sponsors this inquiry, the Medical Advisory Committee and the Editor have, we believe, approached this study objectively and fairly. The possible difference in attitude between these and the contributors is that the Editors have entered upon this study with a definite purpose and possibly with preconceptions, whereas the medical men with equal desire to arrive at a just solution are manifestly bewildered and present no semblance of a united front.

In a foreword, Mr. Curtis Bok explains the method of research in these words:

> "Indeed, we have developed a technique whereby not we but the competent or especially interested groups really do the researching—by which I mean to say that we attach no final value to our personal conclusions, except to the degree to which they are checked and supplemented by the groups throughout the country especially competent to have opinions and information, and to exercise judgment, in a given field. Our procedure is to present problems to competent groups and then to define the problems comprehensively by assembling all the factors brought forward in the free discussion that follows. We do evaluate the ideas, but under stern challenge from our collaborators."

The Chairman of the Medical Advisory Committee, Dr. Truman G. Schnabel, in a brief introduction says in part:

"As in the case of other studies of the American Foundation, the study of the relation of government to health was begun with no assumption either that government should, or that it should not, play a larger part than it now plays in the administration of public health activities, or, so far as the individual citizen is concerned, in the organization of medical care.

"The health study was brought to the fore in our active program, was singled out from other subjects of our research for more intensive consideration both in the research and in the technique of invoking the opinion of selected groups among the public, because the situation seemed to us to be singularly in need of clarification.

"There is a group that believes there are too many physicians and a second group that believes there are too few; and a third group that believes there are too many bad physicians and too few good ones; and a fourth group that believes this whole question is beside the point and that the real need is to insure that every physician licensed to practice is a good one, in which case the law of supply and demand will ultimately operate to control numbers satisfactorily.

"There are proposals for radical change, on the one hand, and tightly knit defense of the status quo, on the other. There are those who are for revolution and those who are for evolution. There are those who are against revolution, and—yes—those who are against evolution and who become apoplectic at mention of need of any change, however minor.

"The whole question is agitated in one quarter as a purely economic problem, in another as a social, in another as a purely professional and scientific. Few indeed have had the vision to see that all these aspects are involved and that no solution resting on only one of these bases and made without reference to the rest can be serviceable.

"We have been aiming at an analysis of the situation that would take all, and not merely some, of the pertinent factors into account. We have not, at this point, been concerned to find solutions for the problem or for any particular part of it. On the other hand, we have wanted to etch in the present picture fully and, by demonstrating its complexity, avoid over-simplificaton in the application of remedies.

"In sending our inquiry to doctors in the first instance there was no assumption that doctors and doctors alone could solve the problem. Social scientists, economists, government administrators are in a position to estimate the needs of the population; they have certainly a contribution to make, and, with this report as a basis, we contemplate extending this inquiry to include it. But it seemed to us that the group best qualified to define the problem in the first instance is the qualified medical men of the country."

The Committee thereupon selected "a representative list of medical men and women that have been in practice 20 years or more. Certainly a broadly representative list covering all groups in the medical profession and all sections of the country." To these men was sent an inquiry in effect as follows:

"Has your experience led you to believe that a radical reorganization of medical care in this country is indicated? If so, in what direction? If you do not believe that radical reorganization is indicated, what, if any, changes or revisions in the present system would you like to see made? What evolutionary possibilities would you stress?"

A similar letter was sent to representatives of a group of doctors with more than five but less than twenty years practice; and also to a third group of young doctors in the first five years of practice.

The report is essentially a compilation of extracts from approximately 5,000 letters from more than 2,000 doctors

in answer to this Committee's inquiries. These were not in the nature of a poll, nor are they susceptible of translation into a composite representation. The Committee clearly disclaims this:

"It will be impossible to read this report profitably unless it is borne constantly in mind that the purpose of our inquiry was not to poll the medical profession upon anything whatever, but rather to assemble ideas, to etch in the whole picture. It is true that the results of the inquiry do indicate roughly certain 'trends', but it is questionable whether anyone could with integrity state these in the form of conclusions.

"Our correspondents wrote frankly because they were not asked for conclusions, and because they were invited to think out loud. They knew we should not list them as advocates or opponents of any idea. They contributed their experience, their impressions, and their observations richly—without positivism. We are endeavoring to present them with a reciprocal lack of positivism, and with no attempt to attach rigid conclusions to fluid thinking.

"The intent and purpose of this report is to illuminate and not to prove. Those who hoped for a numerical report that so many are for 'state medicine' and so many against it will be disappointed.

"The letters are, in the main, the mature and profound and poignantly sincere thought of men in the field who recognize that there is a problem of subtle composition and who would like to see it solved not by facile experimentation on a broad and untried scale but by experiment guided by all the resources both of science and of statesmanship."

The Editor, Esther Everett Lape, in turn stresses the belief that the report is "more than a collection of opinion", though she admits that it lacks "statistical uniformity and completeness". The editorial attempts to summarize varying conceptions are self-styled, "reconnaissance rather than a concluded study". In concluding the Editor says:

"Of outstanding interest to us in the whole project has been the fact that medical scientists, when asked whether change is needed in the present manner of organizing medical care and of planning for the health of the population, tended to reply not by theoretically discussing social and economic proposals but rather by practically analyzing concrete ways and means of advancing medical science, raising the standards of medical practice and improving medical education."

In our own opinion the Editor here touches upon the most significant and impressive thought derived from an understanding reading of these pages. One finds here a composite picture of the doctor, unconsciously etched by himself. It is in essence an authentic etching and is in fact the only unity found in this bewildering assemblage of diverse opinions, though it comes from doctors in every section of this great land, engaged in every type of city and country practice and in every form of endeavor within the medical profession. As we see it, the outstanding features in this self-drawn portrait are the desire to advance and disseminate knowledge of medicine and to provide adequate medical service for the people.

The report includes chapters on the following subjects:

Is Adequate Medical Care Now Available
General Principles that should Underlie the Organization of Medical Care
Medical Education
Specialization
Group Practice
The Place of the Hospital
Public Health Organization
Experimentation—State, County and Community Plans
State Medicine
Health Insurance, Compulsory, Voluntary, Hospital, Industrial
Limited State Medicine and Private Practice

In each chapter numerous individual opinions are quoted, chiefly illustrating editorial summation of group beliefs. By this means, the Editor is to a certain degree successful in regimenting ideas so that twenty-one hundred individuals are arranged in companies and battalions. This most difficult editorial feat is accomplished with fairness as well as dexterity, yet it must be admitted, the Editor has been well advised in warning us that no conclusions can be based with integrity upon so many variants.

Despite the confusion of mind occasioned by so great diversity, there is a remarkable assembly of opinions upon every phase of medical practice which will be of inestimable value in solving the difficult problems now confronting the profession. This report merits careful study not alone upon the part of the medical profession, but by all persons concerned with the vital social and economic problems of the American people. The very confusion which this presentation reveals, serves to accentuate its complexities and interrelations with many fundamental entanglements in our present social system. A study of this report will also tend to clarify the minds of doctors on this most significant subject.

The report which is in two volumes of 1400 pages merits and requires careful study to gain a true appreciation of its great worth. In addition to throwing much light on the principal subject, it constitutes a most valuable reference book by providing interesting side lights on almost every phase of medical practice.

The sponsors, the Editors and the contributors may well be proud of this achievement.

M.A.

LIBRARY NOTES

Death of Mr. Leonard L. Mackall

Consultant in Bibliography

It is with deep regret that we announce the death of Mr. Leonard L. Mackall, at the age of fifty-eight, which occurred on 19 May at Fredericksburg, Va. His health had not been of the best lately, but his many friends were surprised to hear about two months ago that he was stricken with a severe illness. He was born at Baltimore 29 January, 1879, and was educated at Lawrenceville School, Johns Hopkins University, where he obtained his A.B. in 1900, and at the Harvard Law School which he attended for two years. He forsook the law and devoted himself to literature which he studied at the University of Berlin for another two years, became a Fellow of Johns Hopkins University in 1906, and then returned to Europe for work at the University of Jena. From 1916 to 1918 he was Librarian of, and did extraordinarily good work at, the De Renne Georgia Library at Savannah where he lived. In 1921 he became editor of "Notes for Bibliophiles" published in the "Books" section of the Sunday issue of the *New York Herald Tribune.* He continued in this position till his last illness and his scholarly "Notes" were read week by week with avidity by book-lovers.

Mr. Mackall was a member of many learned societies, including the Bibliographical Society, the American Antiquarian Society, the Grolier Club, the American Historical Association, the History of Science Society, the American Association of the History of Medicine and, at the time of his death, was President of the Bibliographical Society of America and the Georgia Historical Society.

His bibliographical learning was truly wonderful and it seemed that he knew the great books and the less important ones in all branches of knowledge. His correspondence must have been enormous, and who is there that received his letters in answer to an inquiry, who will forget the closely packed typewritten page, with important facts

underlined or put in red? Usually there was a postscript placed at the top because there was no room at the bottom! He had an uncanny memory so that not only did he know an author's works and the various editions and indexes and supplementary volumes—often forgotten by some authorities—but he could tell you the wanderings of special copies, their former owners and the sales they had passed through. All this was at his fingers' ends and he would recite it to you over the telephone with all the necessary dates, should you call him up to ask a question. I have known him to go into a library or a book shop at Oxford, set up his typewriter on a tripod before the shelves and write note after note seemingly about any books which he took down. Who else in the world could do that?

Mr. Mackall's bibliographical first love seems to have been Goethe—his correspondence especially. Then one day about 1900 at Baltimore, his friend Dr. W. W. Francis, mentioned that Dr. Osler had just acquired the big volumes of Lavater's *Essays* (1789-1810), knew next to nothing about him, and was waiting for an opportunity to look him up. Whereupon, as Dr. Francis informs me, Mr. Mackall, replied, "I know all about him; he was one of Goethe's correspondents; let me see the books." "Come along", said Dr. Francis, and that was Mr. Mackall's introduction to Osler. Osler promptly nicknamed him "Lavater", in his kindly, playful fashion. And so Mr. Mackall became a medical as well as a general bibliographer; it is his interest in medical books that concerns us here. Soon no one knew as much about the martyr Michael Servetus and his works as Mr. Mackall. He was one of the four men to whom with Lady Osler was entrusted the completion of the catalogue of Sir William Osler's library, *Bibliotheca Osleriana* . . . Oxford at the Clarendon Press, 1929. As was the case with many other libraries, this one was much enriched through him by many gifts of rare books, and odd out-of-the-way items—and a great number of notes. It is largely owing to him that the Servetus collection, to mention only one section of the Osler Library, is so fine. His first published bibliographical contribution to the subject

of Servetus appeared under the modest title of "Servetus Notes" in *Contributions to Medical and Biological Research Dedicated to Sir William Osler, Bart.,* New York, Paul B. Hoeber, 1919, vol. ii, pp. 767-777. This was followed by an article entitled "A Manuscript of the 'Christianismi Restitutio' of Servetus, placing the Discovery of the Pulmonary Circulation Anterior to 1546", *Proc. Roy. Soc. Med.,* London, 1923-24, (March, 1924), vol. xvii, Hist. of Med. Sect., pp. 35-38. Another of his notes on medical works is contained in a letter to the *Journal of the American Medical Association,* 24 Feb., 1923, vol. 80, pp. 572-573, entitled "The Earliest Recognition of Appendicitis—Again." Mr. Mackall had presented both the German original and the English translation of Heister to the Osler Library.

After Sir William Osler's death, Mr. Mackall read a tribute to him in a paper entitled "Sir William Osler", *The Papers of the Bibliographical Society of America,* vol. xiv, Part 1, 1920, pp. 20-32, Chicago [1922]. When the Osler Library was opened at McGill University, he devoted one of his articles to it, "Dedication of the Osler Library", *New York Herald Tribune, Books,* 16 June 1929. Also with Fielding H. Garrison, Harvey Cushing, and E. C. Streeter, he revised and corrected galley proofs of Osler's *The Evolution of Modern Medicine* for publication by the Yale University Press, New Haven, 1921 (second printing 1922).

Many are the stories of his literary "finds" in the catalogues of second-hand booksellers who did not know the rarity of some of their items, or through visits to book shops. At the sale of John Sargent's books, he bought the very volume of Petrarch's *Opera* (1515) which Dr. Welch is fingering as it lies on the table in that artist's well-known portrait of the *Four Doctors.* He graciously presented it in 1927 to the Tudor and Stuart Club of Johns Hopkins University—he knew the interest and value of "association" copies. Not a rich man himself, the richness of his generosity was extraordinary. I am sure he often

bought books merely to make gifts of them to enhance the extent and value of another man's collection; or if he heard that someone lacked a certain volume, he would take it out of his own library (numbering some twelve thousand items), and give it away. Remember that often he had never met his brother-collector or seen the library to which he made the gift, perhaps away off in Europe. And, imagine the astonishment of the recipient on obtaining a long-sought treasure out of the blue sky, as it were! Even if it meant giving it up himself, or asking another man to do so, Mr. Mackall believed that every book should be placed where it would be most appreciated, most useful, and therefore most valuable. One of the happiest days of his life must have been that of 17 October, 1929, when the William H. Welch Medical Library, named after his great friend, was opened at the Johns Hopkins University. With a most characteristic speech, abounding in relevant bibliographical detail, which he called "Six Books" (*Bulletin of the Johns Hopkins Hospital,* Jan. 1930, vol. xlvi, pp. 83-90), he presented the six treasures to the Library. It seemed that he did not have time or the inclination to compile bibliographies himself, perhaps because he spent most of his day helping others.

In 1926 Mr. Mackall was of the greatest help to me in choosing books to show at our exhibition, a catalogue of which was printed with the title *Catalogue of an Exhibition of Early and Later Medical Americana,* N. Y., 1926. He also aided very much with the brief notes which accompany the list. He was always meticulously exact in writing bibliographical references and his advice was to make them even more detailed than seemed necessary; for instance, he liked to include the month of publication of a magazine. He was not overly strict about the order in which facts were given, provided the whole reference was clear.

We continued to make much use of his knowledge and never did he exhibit the slightest reluctance to help; when he aided us in the Rare Book Room, as Miss Annan puts it, he did it simply and with no effort to impress one with his knowledge. It was a red-letter day at the Academy when

he paid one of his occasional visits—they would have been more frequent, but during the past few years he was in New York for but short periods at a time. He advised us about the purchase of volumes and presented others to the Library. Through his help we acquired many reference works and we have never ceased to be grateful to him for telling us of the two volumes of the *Subject-Index of the London Library,* 1909 and 1923.

In 1932, when Dr. Samuel W. Lambert had completed an account of the initial letters used in the great anatomical work of Vesalius, Mr. Mackall told him that Roth had written about the wood blocks found at Munich, (*Arch. f. path. Anat.* [Virchow's] 1895, Bd. 141, pp. 462-478), and so came about the volume for our "History of Medicine Series", *Andreae Vesalii Icones Anatomicae.* He reviewed this volume in an article entitled "Vesalius Illustrated" in *New York Herald Tribune Books,* 22 December, 1935, and added a correction in the issue of 29 December. Just a short time ago, reading by chance of a list of errata which was published for the *Dictionary of National Biography,* I inquired of him and was delighted that he knew all about it. We succeeded in buying a copy so we now have a valuable addition (I think known to comparatively few) to that invaluable work of reference. One of his last kindly acts was to consent to read over and criticize the manuscript of Miss Janet Doe's *Bibliography of the Works of Ambroise Paré,* which is being published for our "History of Medicine Series" by the Chicago University Press.

We were all delighted when in 1930 he consented to become Honorary Consultant in Bibliography to the Academy. By so doing, he honoured us. We have suffered the loss of a wise and generous friend, but he has left behind an example of all that is best in bibliography.

ARCHIBALD MALLOCH.

A Selection of Recent Accessions

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DEATH OF FELLOW

Mc Creery, Forbes Robert, B.S., M.D.; 123 East 40 Street, New York City; received the degree of Bachelor of Science from the College City of New York in 1885 and graduated in medicine from the College of Physicians and Surgeons in 1888; elected a Fellow of the Academy February 2, 1905; died June 29, 1937. He was a Fellow of the American Medical Association and a member of the State and County Medical Societies.

OFFICERS OF SECTIONS, 1937-1938

Dermatology and Syphilology, 1st Tuesday

Chairman	*Secretary*
Louis Chargin	Harry C. Saunders
1 West 85 Street	159 West 87 Street

Surgery, 1st Friday

Roderick V. Grace	Frank L. Meleney
100 East 66 Street	180 Ft. Washington Avenue

Neurology and Psychiatry, 2nd Tuesday

Irving Pardee	Morris Grossman
160 East 64 Street	66 West 87 Street

Historical and Cultural Medicine, 2nd Wed. of Nov. Jan., Mar. and May

Reginald Burbank	Howard R. Craig
6 East 78 Street	175 East 79 Street

Pediatrics, 2nd Thursday

Samuel Z. Levine	Philip M. Stimson
N. Y. Hospital, 525 East 68 Street	25 Claremont Avenue

Ophthalmology, 3rd Monday

James W. White	Rudolph Aebli
15 Park Avenue	30 East 40 Street

Medicine, 3rd Tuesday

Joseph Hajek	Thomas T. Mackie
555 Park Avenue	16 East 90 Street

Genito-Urinary Surgery, 3rd Wednesday

Fedor L. Senger	John A. Taylor
142 Joralemon Street *Brooklyn*	2 East 54 Street

Otolaryngology, 3rd Wednesday

Clarence H. Smith	James W. Babcock
140 East 54 Street	20 East 53 Street

Orthopedic Surgery, 3rd Friday

Earl E. VanDerwerker	Joseph B. L'Episcopo
333 East 43 Street	177 Lafayette Avenue, Brooklyn

Obstetrics and Gynecology, 4th Tuesday

Thomas E. Lavell	Edward H. Dennen
1 East 63 Street	133 East 80 Street

AFFILIATED SOCIETIES

New York Roentgen Society (Affiliated) (3rd Monday)

Leopold Jaches, *Chairman*	R. W. Lewis, *Secretary*
100 East 94 Street	115 East 61 Street

Society for Experimental Biology and Medicine,
(Auspices of Academy) (3rd Wed.)

Philip E. Smith, *President*	A. J. Goldforb, *Secretary*
630 West 168 Street	City College, Convent Avenue and 139 Street

Harvey Society (Affiliated) (Gives 2nd Acad. Stated Meetings, 3rd Thurs.)

Eugene L. Opie, ***President***	McKeen Cattell, *Secretary*
Cornell Med. Col., 1300 York Avenue	Cornell Med. Col., 1300 York Avenue

New York Pathological Society, (Affiliated) (4th Thurs.)

N. Chandler Foot, *President*	Milton Helpern, *Secretary*
N. Y. Hospital, 525 East 68 Street	400 East 29 Street